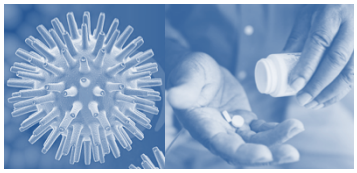

Virus Infections and Drug Hypersensitivity

New Horizons Session 4 – December 4th, 2011,
Cancún, México

Barbara Daubner, PhD

ADR-AC GmbH, Bern & Clinic for Rheumatology and Clinical Immunology/Allergology
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Virus infections and drug hypersensitivity

What is known/speculated?
(Coincidence, aggravation of symptoms)

- Infections in children
  (transient intolerance of antibiotics, in particular amoxicillin)
- Herpes virus infections
- HIV infections

Possible mechanism involved?

- Virus infection – cross-reactivity
- Virus infection – co-stimulation/co-activation

Infections in children

- Many children make a maculopapular exanthema after amoxicillin and other drugs

- Skin tests and provocation test later often negative

Coincidence of
viral infection and drug exposure

Infections in children

Which viruses are implicated?

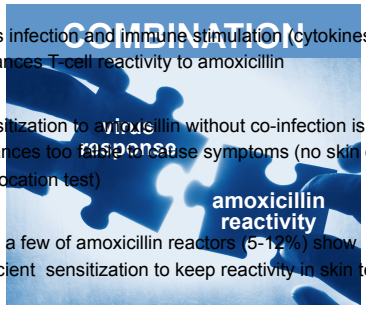
Picorna-, Corona-, Boca-, Influenza-, Parainfluenzavirus, RSV, Human Metapneumovirus (hMPV)

detectable in ca. 66%* of children with β-lactam and exanthem („rash“, delayed urticaria)

* Caubet et al. JACI (2011) 127:218

“It is not a hypersensitivity reaction, but a consequence of virus infection”

- Virus infection and immune stimulation (cytokines) enhances T-cell reactivity to amoxicillin
- Sensitization to amoxicillin without co-infection is in most instances too rarely to cause symptoms (no skin or provocation test)
- Only a few of amoxicillin reactors (5-12%) show sufficient sensitization to keep reactivity in skin test



Herpesvirus infections

Cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus-6 and -7 (HHV-6/HVV-7), Herpes simplex virus (HSV)…

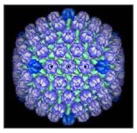
- active: e.g. in infectious mononucleosis

- persistent: >10% of T-cells involved in control of endogenous herpesviruses

- reactivating: e.g. in DRESS or MDH (Multiple Drug Hypersensitivity)

Herpesvirus infections - IM

Infectious Mononucleosis (IM)



EBV infection

drug:

ampicillin
penicillin
amoxicillin

skin eruption:

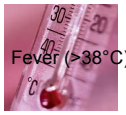
incidence between 42 – 100%

Herpesvirus infections - Diagnostic criteria for DIHS/DRESS

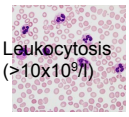
1 Maculo-papular rash >3 weeks after therapy

2 Lymphadenopathy

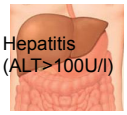
3 Fever (>38°C)



4 Leukocytosis (>10x10^9/l)



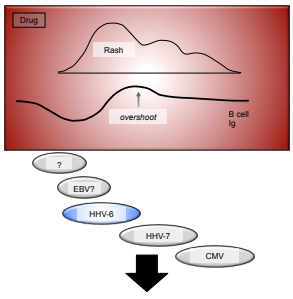
5 Hepatitis (ALT>100U/l)



6 HHV-6 reactivation

(Shiohara T. Allergol Int (2006) 55:1-8)

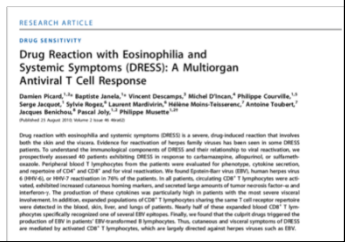
Herpesvirus infections - Sequential reactivation of herpesviruses in DIHS/DRESS *(adapted from Shiohara & Kano, (2007) Clinic Rev Allerg Immunol)*



clinical symptoms might be triggered by sequential virus reactivation

Herpesvirus infections – DRESS: A multiorgan immune response

"…cutaneous and visceral symptoms of DRESS are mediated by activated CD8⁺ T lymphocytes, which are largely directed against herpes viruses such as EBV ".



RESEARCH ARTICLE

DRUG SENSITIVITY

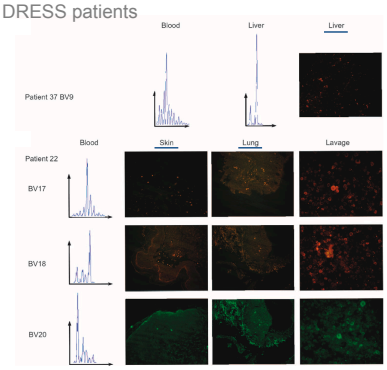
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): A Multiorgan Antiviral T Cell Response

Damien Picard,[1,2]* Baptiste Janela,[1]* Vincent Descamps,[3] Michel D'Incan,[4] Philippe Courville,[1,5] Serge Jacquet,[1] Sylvia Rogez,[6] Laurent Mardivirin,[6] Hélène Moins-Teisserenc,[7] Antoine Toubert,[7] Jacques Benichou,[8] Pascal Joly,[1,2] Philippe Musette[1,2]†

Published 21 August 2010; Volume 2 Issue 46 46ra62

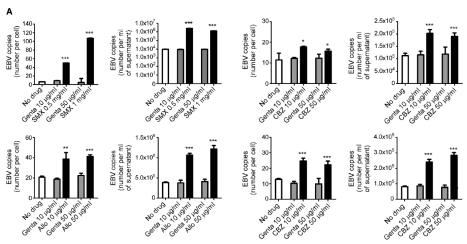
Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe, drug-induced reaction that involves both the skin and the viscera. Evidence for reactivation of herpes family viruses has been seen in some DRESS patients. To understand the immunological components of DRESS and their relationship to viral reactivation, we prospectively assessed 40 patients exhibiting DRESS in response to carbamazepine, allopurinol, or sulfamethoxazole. Peripheral blood T lymphocytes from the patients were evaluated for phenotype, cytokine secretion, and repertoire of $CD4^+$ and $CD8^+$ and for viral reactivation. We found Epstein-Barr virus (EBV), human herpes virus 6 (HHV-6), or HHV-7 reactivation in 76% of the patients. In all patients, circulating $CD8^+$ T lymphocytes were activated, exhibited increased cutaneous homing markers, and secreted large amounts of tumor necrosis factor–α and interferon-γ. The production of these cytokines was particularly high in patients with the most severe visceral involvement. In addition, expanded populations of $CD8^+$ T lymphocytes sharing the same T cell receptor repertoire were detected in the blood, skin, liver, and lungs of patients. Nearly half of these expanded blood $CD8^+$ T lymphocytes specifically recognized one of several EBV epitopes. Finally, we found that the culprit drugs triggered the production of EBV in patients' EBV-transformed B lymphocytes. Thus, cutaneous and visceral symptoms of DRESS are mediated by activated $CD8^+$ T lymphocytes, which are largely directed against herpes viruses such as EBV.

EBV-specific CD8⁺ T cells in blood, skin lesions, liver, and lungs of DRESS patients



Picard et al. Sci Transl Med (2010)

Induction of EBV by culprit drugs



Picard et al. Sci Transl Med (2010)

Definition of MDH:

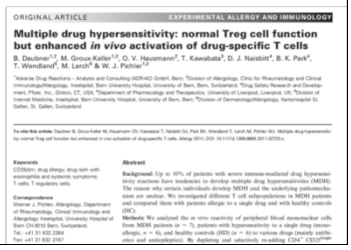
Multiple drug hypersensitivity (MDH) patients

- Typical medical history of drug allergy (starts often with a severe hypersensitivity reaction like a DRESS)
- > 1 non cross-reacting drug
- positive in skin or/and *in vitro* tests (LTT)

Daubner et al. (2011) Allergy

Herpesvirus infections – MDH: triggered by viral co-stimulation?

"…A particular feature of DMH is the fact that the drug-reactive T cells are found in an *in vivo* pre-activated cell fraction".



ORIGINAL ARTICLE EXPERIMENTAL ALLERGY AND IMMUNOLOGY

Multiple drug hypersensitivity: normal Treg cell function but enhanced *in vivo* activation of drug-specific T cells

B. Daubner[1,2], M. Grioux-Keller[1,2], O. V. Hausmann[3], T. Kawabata[4], D. J. Naisbitt[4], B. K. Park[4], T. Wendland[5], M. Lerch[6] & W. J. Pichler[1,2]

[1]Adverse Drug Reactions – Analysis and Consulting (ADRAC) GmbH, Bern, [2]Division of Allergology, Clinic for Rheumatology and Clinical Immunology/Allergology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland, [3]Drug Safety Research and Development, Pfizer, Inc., Groton, CT, USA, [4]Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, UK, [5]Division of Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, [6]Division of Dermatology/Allergology, Kantonsspital St. Gallen, St. Gallen, Switzerland

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Keywords
CD25dim; drug allergy; drug rash with eosinophilia and systemic symptoms; T cells; T regulatory cells.

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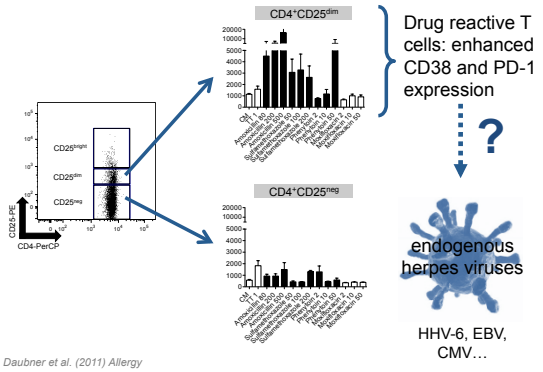
Abstract

Background: Up to 20% of patients with severe immune-mediated drug hypersensitivity reactions have tendencies to develop multiple drug hypersensitivities (MDH). The reason why certain individuals develop MDH and the underlying pathomechanisms are unclear. We investigated different T cell subpopulations in MDH patients and compared them with patients allergic to a single drug and with healthy controls (HC).

Methods: We analyzed the *in vitro* reactivity of peripheral blood mononuclear cells from MDH patients ($n = 7$), patients with hypersensitivity to a single drug (mono-allergic, $n = 6$), and healthy controls (HD) ($n = 6$) to various drugs (mainly antibiotics and antiepileptics). By depleting and selectively re-adding $CD4^+$ $CD25^{high}$

Drug-reactive T cells in $CD4^+CD25^{dim}$ subpopulation



Daubner et al. (2011) Allergy

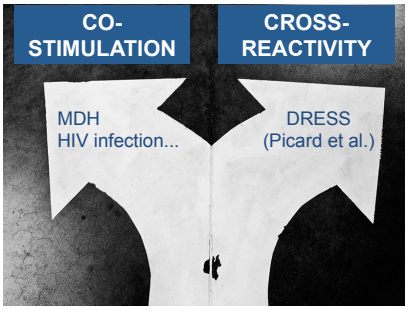
HIV infections

HIV infected patients

- Sulfonamide hypersensitivity reactions (increased incidence from 4% in normal population up to 60%*[1] or higher in HIV$^+$ population)
- Probability to develop SJS/TEN: 1000-fold*[2] higher!
- Other drug allergies ?

*[1] Jaffe et al. Lancet (1984) 2:1109–1111
*[2] Eliaszewicz et al. J Am Acad Dermatol (2002) 47:40–46

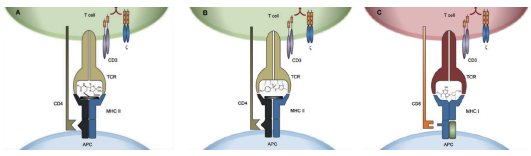
Possible mechanism involved?



Co-stimulation

p-i concept

(pharmacological interaction with immune receptors)



hapten concept

p-i-concept

A) Antigenic hapten-carrier complexes induces T cell responses

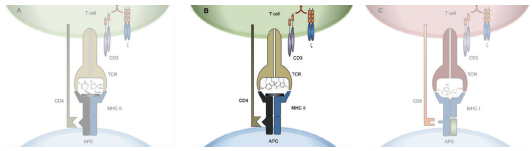
Drugs bind directly…
B) to the TCR
C) to the MHC

Adam J. et al. BJCP (2011) 71(5):701-7

Co-stimulation

p-i concept

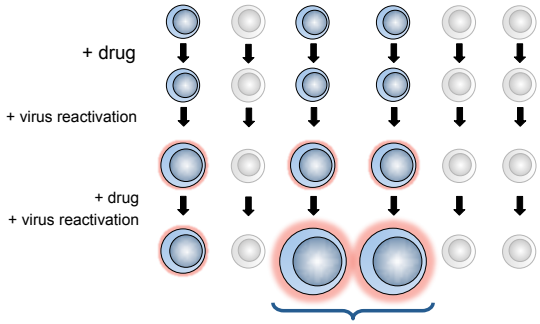
(pharmacological interaction with immune receptors)



Pre-activation is needed!

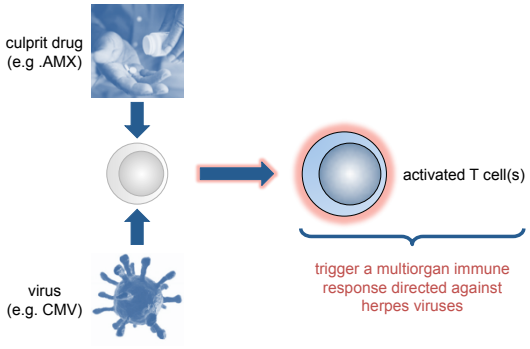
Co-stimulation

T cell repertoire (2.5×10^7)



A) Herpesvirus reactivation leads to activated virus-specific T cells
B) Drug binds to (pre-) activated virus-specific T cells (trigger!)

Cross-reactivity



trigger a multiorgan immune response directed against herpes viruses

SUMMARY

- Viruses are activating a broad repertoire of T cells; this activation enhances the response to drugs and facilitates T cell mediated drug allergies (exanthems, hepatitis, DRESS, ...).
  - This activation occurs in children (probably caused by different viruses); *transient exanthema* to drugs in childhood
  - It occurs during adulthood: the chronic herpes viruses (EBV, CMV, HHV-6) are activating T cells (*exanthema, DRESS*)
- Involved mechanism:
  - Activation of virus-specific T cells -> drug binds to this pre-activated T cell **(co-stimulation)**
  - drug/virus-cross-reactive T cells **(cross-reactivity)**

Prof. Werner J. Pichler

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